REMARKS

With the entry of this amendment, claims 16 and 18-43 are now pending in this application. Claims 16-31 have been rejected. Applicants thank the Examiner for withdrawing the prior obviousness rejection in light of Applicant's response filed on October 16, 2002. Applicants submit a terminal disclaimer and the requisite fee with this response. Additionally, Applicants submit an Information Disclosure Statement and a PTO Form-1449 along with copies of the references cited.

Applicants cancel claim 17 without prejudice. Applicants amend claims 23 and 24 and add new claims 32-43 to more clearly describe the invention. No new matter has been added by these amendments. Support for the claim amendments and new claims 32-43 may be found in the original claims as well as in the specification on page 8, line 5 through page 9, line 22. Applicants respectfully submit that claims 16 and 18-43 are allowable in view of these amendment and remarks.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 23 and 24

The Examiner rejected claims 23 and 24 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification.

Claims 23 and 24 are directed to antibodies of the invention that bind a subunit of the IL-12 heterodimer. The Examiner acknowledges that the specification is enabling for a method of using an IL-12 antibody to treat rheumatoid arthritis. However, the Examiner alleges that the specification fails to enable a method of using an antibody

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that *only* binds to either the 40 kD subunit or the 35 kD subunit of IL-12. Specifically, the Examiner contends that the Applicants "have pointed to portions of the specification for support that appear to be a mere paper protocol for a method of treating RA that administers an antibody that binds to a 40 kD or 35 kD subunit of IL-12." Office Action, at 4. Lastly, the Examiner cites *Kim et al.* (Clin. Exp. Immunol. 119:175-181 (2000)) (hereafter "*Kim*") as teaching that neither of these (35 kD or 40 kD) subunits has been found to display any significant biological function *alone*.

Applicants respectfully traverse this rejection. Without acquiescing to this rejection, and only to clarify the scope of the claims 23 and 24, which depend on claim 16, Applicants amend claims 23 and 24 to more clearly describe the invention. Specifically, amended claims 23 and 24 now recite that the antibody that binds IL-12, binds to an epitope on a 40 kD subunit of IL-12 or a 35 kD subunit of IL-12, respectively. Applicants respectfully submit that independent claim 16, from which claims 23 and 24 depend from, recites that the antibody binds IL-12. Thus, claims 23 and 24 further describe binding of the antibody to IL-12. Claims 23 and 24 merely recite that the antibody binds to a subunit of IL-12 in the context of the IL-12 heterodimer comprising the 40 kD and the 35 kD subunits. Neither claim 23 nor claim 24 require that the antibody bind the 40 kD or the 35 kD subunit alone. Accordingly, Applicants submit that none of claims 23 or 24 require that the antibody bind only the 40 kD or the 35 kD subunit of the IL-12 heterodimer.

However, binding of an antibody to a single subunit alone, either the 40 kD or the 35 kD subunit is encompassed by this invention and has been enabled by the

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specification. If, for example, an antibody bound to the 40 kD subunit, it could prevent the formation of a heterodimer containing the 40 kD subunit. It could also bind the 40 kD subunit in such a way as to still allow heterodimer formation, but inhibit activity of the heterodimer. None of these functions depend on independent activity of the 40 kD subunit or the other subunit in a heterodimer, but relate to the fact that the presence of an unhindered 40 kD subunit is essential to the function of a heterodimer containing that subunit. The Examiner cites to *Kim* for the proposition that the p40 and p35 subunits have no significant biological function as monomers. This bolsters Applicants' argument that an antibody that sequesters the 40 kD subunit and prevents binding of the 40 kD subunit in a heterodimer, would be effective in the treatment of rheumatoid arthritis, as neither subunit in IL-12, for example, has biological activity alone.

In view of the foregoing, Applicants respectfully submit that claims 23 and 24 are enabled by the specification and respectfully request that this rejection be reconsidered and withdrawn.

Claims 30 and 31

The Examiner rejected claims 30 and 31 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. While the Examiner acknowledges that the specification is enabling for a method of using IL-12 to treat rheumatoid arthritis, the Examiner alleges that the specification is not enabling for combination therapies using IL-12 antagonists in combination with other therapies for autoimmune conditions, and therapies for autoimmune conditions comprising steroidal or other anti-inflammatory therapies. The Examiner contends that the art is not clear with regard to combination

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therapies, which includes anti-IL-12 antibodies for the treatment of rheumatoid arthritis. Office Action, at 5. As an example, the Examiner cites *Jaffe* as teaching that some combination therapies have not been successful. In addition, the Examiner cites *Borigini et al.* and *Verhoeven et al.* as teaching that there are obstacles associated with the establishment, evaluation, and approval of combination drug therapies. In view of these issues, the Examiner alleges that there would be undue experimentation for a skilled artisan to practice the claimed invention.

Applicants respectfully traverse this rejection and submit that the references cited in the Office Action are misleading and not relevant to the specific **biological therapy** at hand. Specifically, *Jaffe* only teaches combinations of standard elemental or small molecule antirheumatic and chemotherapeutic drugs (e.g., combinations of gold, hydroxychloroquine, and D-hydroxychloroquine, respectively). These classes of **chemical agents** are well known to cause many adverse side effects and drug-drug interactions (due to, e.g., alterations in drug metabolism) that may account for their decreased efficacy and increased toxicity when used in combination. Many of the adverse side effects of chemical agents are caused by their interactions with non-specific targets. In contrast, monoclonal antibodies (such as those disclosed in this application) are **biological agents** that target a particular ligand and are much more specific because they have a single target (i.e., IL-12). As such, they cannot cause the same wide scope of adverse effects as prior chemical agents. There is no suggestion in *Jaffe* that combination therapy involving an anti-cytokine antibody (or any other non-chemical, biological agent) and another anti-inflammatory agent would be unsuccessful due to drug

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interactions or increased adverse effects (as was observed with combination therapy involving only chemical agents).

Applicants further submit that *Borigini* and *Verhoeven* should not be used as evidence that the art is not clear regarding combination therapies involving anti-IL-12 or other anti-cytokine antibodies. Like *Jaffe*, *Borigini* and *Verhoeven* only teach typical **chemical antirheumatic drugs** (e.g., gold, methotrexate, hydroxychloroquine, azathioprine, D-penicillamine, and sulphasalazine) and emphasize that the use of these agents is limited by their toxicity. In fact, the use of combination therapy involving these chemical agents is an alternative approach to inadequate or short-lived single drug therapy. *Borigini* at 691. The factors cited by the Examiner as having retarded progress in the search for successful combinations of antirheumatic drugs are directly related to the known toxicities of these drugs. *Borigini* reports that combinations that include **biological agents** are useful, stating:

> It is also important to continue the development of so-called **'biological agents'**, such as interleukin-2 receptor antibodies, anti-CD4 antibodies, anti TNF-*α* agents and antithymocyte globulin. Combinations which include such agents have not yet been evaluated, although it seems logical considering that these agents offer the possibility of **precise intervention** directed at specific steps of the immuno-inflammatory process; their combination may thus be **more effective** than the use of single agents alone.

Borigini at 707 (emphasis added). Thus, *Borigini* even sets biological agents apart.

Applicants further advise that another anti-cytokine antibody (anti-TNF-α) has been used successfully to treat rheumatoid arthritis patients that were unresponsive to most drugs. In this study, patients continued maintenance therapy with corticosteroids.

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The Croonian Lecture 1995, J. Royal Coll. Phys. London., 30:344-351 (1996). (Applicants herewith submit a courtesy copy of this reference that was previously cited by the Examiner on a PTO-Form 892, as part of Paper No. 20, in the instant application). Therefore, the skilled artisan or physician would be able to similarly use IL-12 antagonists in combination with other therapies without undue experimentation. The skilled artisan or physician would be able to determine dosage and treatment schedules based on other studies of anti-cytokine (or anti-cytokine receptor) antibodies and anti-inflammatory and steroidal compounds, and would be able to optimize protocols using standard pharmacological approaches. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Obviousness-type Double Patenting Rejection

The Examiner provisionally rejected claims 16-31 under the doctrine of obviousness-type double patenting as being unpatentable over claims 16-20 of co-pending U.S. Application No. 09/512,930.

Solely in an effort to expedite prosecution, and not acquiescing to this rejection, Applicants enclose a Terminal Disclaimer, along with the requisite fee. Accordingly, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that claims 16 and 32-43 are fully enabled by the specification. Applicants therefore respectfully

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request the reconsideration and withdrawal of the rejections and the timely allowance of the pending claims. Should the Examiner not believe that the claims are in condition for allowance, Applicants request that she please contact their undersigned representative at (202) 408-4086 for an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 23, 2002

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APPENDIX TO THE AMENDMENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Amended) The method of claim 16, wherein the antibody that binds to IL-12, binds to an epitope on a 40 kD subunit of IL-12.

24. (Amended) The method of claim 16, wherein the antibody that binds to IL-12, binds to an epitope on a 35 kD subunit of IL-12.

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